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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,296	03/13/2001	Vladimir Efimov	AM-00102.P.1-US	2109
24232	7590	01/22/2004	EXAMINER	
DAVID R PRESTON & ASSOCIATES 12625 HIGH BLUFF DRIVE SUITE 205 SAN DIEGO, CA 92130			MCKENZIE, THOMAS C	
			ART UNIT	PAPER NUMBER
			1624	

DATE MAILED: 01/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/805,296	<b>Applicant(s)</b> EFIMOV ET AL.	
	<b>Examiner</b> Thomas McKenzie, Ph.D.	<b>Art Unit</b> 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 October 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 97-129 is/are pending in the application.
- 4a) Of the above claim(s) 97-107 and 114-129 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 108-113 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>4</u> | 6) <input type="checkbox"/> Other: _____                                    |

**DETAILED ACTION**

1. This action is in response to amendments filed on 10/21/03. Applicant has amended claims 108-111. There are thirty-three claims pending and six under consideration. Claims 108-113 are compound claims. This is the second action on the merits. The application concerns some nucleobase compounds linked to a 4-hydroxyproline and uses thereof.

***Response to Amendment***

2. The file is now in scanned form and the references discussed in point #5 of the previous office action have been, in main part, located. Applicants' new title overcomes the objection made in point #8. Applicants' deletion of the formula containing the N-T radical from claim 108 overcomes the indefiniteness rejections made in points #10, #11, and #18 as well as the enablement rejections made in points #26-#28. Applicants' deletion of "a nucleobase-binding group" from claim 108 overcomes the indefiniteness rejection made in point #16. Applicants' deletion of the relevant material overcomes the indefiniteness rejections made in points #19 and #20. Applicants' deletion of the relevant material from claim 109 overcomes the indefiniteness rejections made in points #21 and #22 as well as the enablement rejection made in point #29. Applicants' incorporation of the needed structures overcomes the indefiniteness rejection made in point #23.

***Election/Restrictions***

3. Claims 97-107 and 114-129 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14.

4. Objection remains to claims 108-113 as containing non-elected subject matter. The claimed compounds, compositions, and methods that employ them present a variable core. Formula of claim 108 contains compounds drawn to the non-elected inventions to the extent it reads on compounds other than B<sup>2</sup> = a purine or a pyrimidine.

Applicants make no remarks concerning this objection.

***Specification***

5. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486

F.2d 577, 179 USPQ 167 (CCPA 1973). The issue concerning the PCT applications and the meaning of "non-naturally occurring nucleobase" is discussed below.

Applicants remark that the material is not essential and in any event the term is definite. This is not persuasive, for patentability issue is at stake, and the Examiner has maintained the indefiniteness rejection below.

6. The possible use of the trademarks Cy3 and Cy5 is discussed below. They should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Applicants remarked that they wish to hold this in abeyance.

#### **Abstract**

7. Applicant is still reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral

anti-diabetics." The abstract is too generic. Examiner suggests claim 108, including the figure.

Applicants remark that they wish to hold this in abeyance.

***Claim Rejections - 35 USC § 112***

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 108-113 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The elected subject matter of claim 108 includes radical B<sup>1</sup> selected from "a non-naturally occurring nucleobase, an aromatic moiety, a DNA intercalator, a nucleobase-binding group, a heterocyclic moiety, or a reporter group". These five terms are indefinite because it is unclear what are the structures of the claimed radicals.

Applicants define "non-naturally occurring nucleobase" in lines 5-17, page 14 of the specification. The definition uses open language "such as" and "can be". Applicants list a number of bases not found in natural nucleosides in lines 9-14, page 14. What bases in addition to these are being claimed? The passage cited incorporates by reference two US Patents and four PCT applications. While US Patents may be incorporated by reference, PCT applications may not. Search of the two US Patents, reveals no usage of the phrase "non-naturally occurring

nucleobase". In lines 18-23, column 5 of US Patent 6,150,510 there is a definition of "unnatural bases". The definition also uses open language "such as, for example". All of the specific radical listed in the passage cited appear to be incorporated into Applicants' list. What additional radicals are being incorporated from US Patent 6,150,510?

Applicants argue that the xanthine and 2-aminoadenine are included and point to the specification page 14, lines 5-18. They also refer to US Patent 5,432,272 as defining the term. This is not persuasive. Is the term limited to xanthine and 2-aminoadenine? In the previous action, the Examiner asked for a list of bases included in the definition. If Applicants cannot answer the question, then how will the public be expected to understand the metes and bounds of the claims? The use of open language in the passage cited by Applicants was discussed in the original rejection. The Examiner could not find the term "non-naturally occurring nucleobase" in the cited documents during the first action. He has search again and again cannot find the term. Where in the text of US Patent 5,432,272 is it found? The US Patent 5,432,272 does contain the word "unnatural bases". This is hardly the same as the phrase used by Applicants. An unnatural base includes "purine, 8-azapurine, 2,6-diaminopurine, 7-deazaadenine, 7-deazaguanine, 4 -ethanocytosine, 6 -ethano-2,6-diaminopurine,

pseudoisocytosine, 5-methylcytosine, 5-fluorouracil, 6-alkynyluracil, and 6-alkynylcytosine. Are these all or are there more?

9. Claims 108-113 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner can find no definition of "aromatic moiety" in the specification. Aromatic is a chemical property. It refers to compounds which conform to Huckel's rule and contain 6, 10, 14, 18 etc  $\pi$  electrons in a ring system. It could refer to all carbon rings or to rings containing non-carbon atoms. Does "aromatic moiety" include heteroaryl compounds like pyridine and purine or are only hydrocarbons intended? Cyclopentadiene anion, cyclooctatetrene dianion, cyclopropenyl cation, and cycloheptatrienyl cation are considered by some to be aromatic hydrocarbons. Are these intended?

Applicants argue that this is an art recognized term and that both carbon-only ring structures and heteroaryl compounds are intended. Yet Hawley (The Condensed Chemical Dictionary) restricts the term to hydrocarbons. A secondary meaning is perfume chemicals with a pleasant smell. Surely this cannot be Applicants meaning? Hawely distinguishes aromatic compounds from the heteroaryl compound furan, yet Applicants would include furan in their broad



meaning. How can the term be art recognized to include heteroaryl compounds when the standard dictionary says it does not?

10. Claims 108-113 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner can find no definition of "heterocyclic moiety" in the specification. There are inconsistent and differing uses of the word heterocycle in the chemical arts. The widely used textbook "Organic Chemistry" by Fessenden says on page 451 that the compounds must be aromatic but that any and all of the atoms in the ring may be selected from the entire periodic table. The widely used "Condensed Chemical Dictionary" also implies that a heterocycle must be aromatic but that only 5 or 6 membered ring compounds with sulfur or nitrogen, not every possible atom are included in the meaning of 'heterocycle'. The less widely used textbook "Introduction to Organic Chemistry" by Streitwieser on page 1061 defines 'heterocycles' as both aromatic and nonaromatic. It further implies that the nitrogen, oxygen, and sulfur atoms are commonly meant and that any size ring falls under the sense of the word. The US Patent Office in the classification definitions does not consider a ring consisting of carbon and phosphorus to be a heterocycle but Hackh's (Chemical Dictionary) lists phosphorus as one of six permissible heteroatoms. Does heterocycle refer only to

aromatic compounds or are saturated compounds like piperidine also included? Is a ring containing carbon and phosphorus a "heterocyclic moiety"? Is it only 5 and 6-membered ring compounds or is homopiperazine included? Are oxygen containing rings included? How about chlorine or boron?

Applicants argue that the term is art recognized and that both aromatic and those that are not are intended. Again how can the term be art recognized when there is wide disagreement in basic chemical dictionaries and college textbooks as to what the term means? Again the Examiner asked a number of questions about what Applicants intend to include by this term. If Applicants cannot answer the question, then how is the public to understand the intended scope of the claim?

11. Claims 108-113 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In lines 3-8, page 16 Applicants define "intercalator" as " a chemical moiety that can bind a nucleic acid molecule or a nucleic acid analogue molecule by inserting between adjacent nucleobases." DNA is a type of nucleic acid molecule but of course is not the only type. Are all "intercalator" molecules DNA intercalators or just some of them? How is the intercalation measured? How large must the associate constant be for an intercalator to be considered bound to the DNA? Must they intercalate all DNA

molecules or just some? Could a radical that intercalates only one unique DNA sequence be included? How many DNA molecules must be screened before a potential infringer can conclude that the radical does not intercalate DNA? In lines 4-8 Applicants list some possibilities using open terms, "non-limiting". What else is intended? The molecule quinoline is listed in the singular but dihydroquinones are plural. What does that imply? Are only para dihydroquinones intended or are ortho-dihydroquinones also included? Are these dihydrobenzoquinones or could they be naphthoquinone and anthroquinone also?

Applicants argue that page 16, lines 5-8 lists specific, non-limiting examples of intercalators. They also argue "in order to claim a genus, one is not required to list every species, even if known. Instead, it is sufficient to provide representative examples in order to cover the genus." This is not persuasive. The open terms used in the definition were discussed above. Applicants are not claiming a genus. They are claiming radicals by one specific chemical property independent of the radical structure. Yet nowhere is there direction of how to measure this property or what threshold of intercalation is required for a radical to be included in the definition. In *Ex parte Anderson* USPQ2d 1241 functional terms were held to be indefinite when there was no disclosure of either any method of measuring the

property or any mention of the specific values this property need have when determining infringement and domination issues.

12. Claims 108-113 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants define "reporter group" in lines 9-18, page 16 again using open language. We are taught it is any group "directly or indirectly detectable". Detectable how and with what sensitivity? What does indirectly detectable mean? The list of specific molecules found in lines 10-18, page 16 is exactly that, molecules, not the univalent radical required of B<sup>1</sup>. How are these molecules to be attached to the claimed core structure since they lack any free valances? Both **CY3 DIRECT<sup>®</sup>** and **CY5 DIRECT<sup>®</sup>** are registered trademarks of AMERSHAM BIOSCIENCES for fluorescent dyes for labeling nucleotides and proteins for scientific and research use. Is this all that is intended in line 14, page 16? If not, what?

Applicants make no argument concerning the meaning of term and ask that the trademark issue be held in abeyance.

13. Claims 110 and 111 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "a phosphono

peptide nucleic acid monomer" is indefinite. Again, nowhere in the specification is this term defined *verbatim*. What is the structure of this radical? In lines 24-27, page 2 Applicants introduce the abbreviation "pPNAs" for phosphono peptide nucleic acid. In lines 16-19, page 12, Applicants define "a phosphono peptide nucleic acid" but fail to specify if this is a monomer. They use open language "comprising" "such as". In lines 23-26, page 13, Applicants define "monomer unit of a peptide nucleic acid" but fail to specify if this is a phosphorus containing peptide. The definition includes "nucleobase (or nucleobase analogue, nucleobase-binding unit, ligand, intercalator, reporter group or label)". The indefiniteness of these terms has been discussed above. The nucleobase "is covalently attached to an amino acid or amino acid derivative or analog". Does amino acid refer to the twenty naturally occurring amino acids, which are coded for in DNA, or are all compounds containing any acid and amine group intended? The issue of derivative or analogue was discussed previously. The three structures **II-IV**, pages 20, 22, and 24 are described as hydroxyproline and aryl phosphono peptide nucleic acid monomers. Is this what is meant? The Examiner understands that hydroxyproline is an amino acid, which may be incorporated into a peptide, but itself is not a peptide. An aryl group is not a peptide but structure IV apparently

may contain additional peptides in radicals G and E. The Examiner suggests using structures **II-IV**, if that is what is intended.

Applicants argue that these are art recognized terms and that " that PNAS, like nucleic acids, are assembled from smaller building blocks, frequently monomers such as phosphono peptide nucleic acid monomers in the case of PNAS, and nucleotides in the case of nucleic acids." This is not persuasive. Assertion that these are art-recognized terms is not evidence. Are there dictionaries or biochemistry textbooks that define the terms? An Internet Google search reveals the following definition for phosphonopeptides, "\*\*\*peptides in which an amide bond is replaced with a phosphonate linkage". This is not Applicants' intended meaning, which is some kind of derivative of a nucleic acid and not a peptide derivative. Could "a phosphono peptide nucleic acid monomer" include nucleic acid monomers to which a phosphono peptide has been attached? While pPNAs polymers are assembled from monomer units, what exactly are these monomers? The issue is the structure of the monomer units since the phrase includes the word monomer. The open language "such as" has been discussed above.

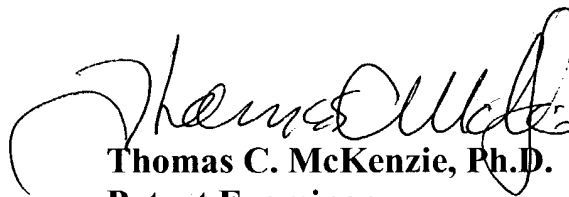
14. Claim 112 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. The indefiniteness of "nucleobase" generally as including non-naturally occurring nucleobases was discussed above.

Applicants' argument concerning this rejection and the Examiners' response were discussed above.

***Conclusion***

15. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. After February 5, 2004, the Examiner may be reached at (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

  
**Thomas C. McKenzie, Ph.D.**  
**Patent Examiner**  
**Art Unit 1624**

TCMcK